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Acute Hemorrhagic Pericarditis in a Child with Pneumonia Due to *Chlamydophila pneumoniae*

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***Chlamydophila pneumoniae* is mainly responsible for respiratory tract infections but has also been associated with endocarditis and myocarditis. We report a case of pneumonia in a child with hemorrhagic pericardial effusion with a positive result by a new *C. pneumoniae* TaqMan PCR, suggesting a pericardial inflammation directly induced by *C. pneumoniae*. *C. pneumoniae* should be suspected in patients with community-acquired pneumonia and concurrent pericarditis. Empirical treatment with azithromycin seems feasible.**

CASE REPORT

A 13-year-old girl presented with tachypnoea and shortness of breath that was exacerbated by exertion. These symptoms worsened during the last 24 h prior to admission. In addition, she complained of throat pain and nausea. There was a history of skeletal dysplasia of unknown cause, scoliosis, generalized gingivitis, and mild aortic-valve regurgitation. No other symptoms of note were elicited, and no medication was concurrently taken.

On examination, the patient was subfebrile (38.3°C) and pale. She had severe shortness of breath when lying supine but was only mildly dyspnoeic when sitting forward. The first and the second heart sounds were soft, and no murmur was heard. Coarse crackles were found on auscultation of both lungs. Abdominal palpation was painful in the epigastrium and left upper quadrant. Hematological investigation revealed a white cell count of 12.6×10^9/liter. C-reactive protein was 20 mg/liter. Blood gases were normal. A chest X ray showed central bilateral infiltration and an enlarged cardiac silhouette (Fig. 1). Echocardiography revealed pericardial effusion (Fig. 2). On admission, empirical antibiotic therapy with azithromycin for community-acquired pneumonia was initiated.

Known causes of pneumonia and myocarditis or pericarditis were excluded. No serological evidence of acute infection with influenza virus, parainfluenza virus, Epstein-Barr virus, adenovirus, varicella zoster virus, coxsackie virus, mumps, measles, echovirus, leptospira, listeria, streptococci (streptolysin negative), staphylococci (staphylolysin O negative), or *Mycoplasma pneumoniae* was found.

On the second day the patient deteriorated clinically; she needed oxygen supplementations, and the pericardial effusion increased in a repeated ultrasound study. Consequently, subxiphoidal pericardial drainage was performed and 500 ml of hemorrhagic effusion was removed. Culture of the pericardial effusion remained sterile, and cytological investigation revealed no malignant cells. The pericardial drain was left for 4 days, and additional antibiotic treatment with cefuroxime was given intravenously for 4 days; anti-inflammatory therapy with ibuprofen was also given. At 3 weeks after removal of the pericardial drain, effusion did not reaccumulate and the clinical status improved. The patient was discharged from the hospital after 14 days. Further serologic workup revealed positive immunoglobulin G (IgG) and IgA antibody results for *Chlamydophila pneumoniae*. For *C. pneumoniae* serology we used sandwich enzyme-linked immunosorbent assays (sELISAs) Medac (Wedel, Germany) for IgG and IgA. The sELISAs and calculations were performed according to the manufacturers' instructions. Finally, we performed a new *C. pneumoniae* TaqMan PCR with the pericardial fluid to verify whether *C. pneumoniae* was directly involved in induction of the infection and especially the hemorrhagic pericarditis (Fig. 3).

The collected pericardial fluid was immediately transported to the diagnostic laboratory at room temperature and stored at 4°C up to the time of DNA preparation. DNA preparations were stored at −20°C. DNA was prepared from two different samplings of the pericardial effusion by use of a QIAamp DNA Mini kit (QIAGEN, Hilden, Germany) and simultaneously subjected to TaqMan PCRs specific for the atypical pneumoniae-causative organisms *M. pneumoniae* (P1 adhesin gene), *Legionella pneumophilia* (*mip* gene), and *C. pneumoniae* (*rpoB* gene).

As an external positive control, a 70-bp conserved region of the human GAPDH gene was amplified (data not shown). The reactions were performed in a final volume of 25 μl containing 0.3 μM concentrations of each primer, 0.2 μM fluorogenic probe, and 25 ng of DNA in one-fold TaqMan MasterMix, which contains 0.25 U of uracyl-*N*-glycosylase (Eurogentec, Seraing, Belgium). PCR procedures were performed under standard conditions (10 min at 50°C, 10 min at 95°C, and 40 cycles of 15 s at 95°C and 1 min at 60°C) with an iCycler (Bio-Rad Laboratories, Hercules, Calif.).

As DNA standards for the PCRs, plasmids encompassing the amplified regions of the different TaqMan PCRs were

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FIG. 1. Enlarged cardiac silhouette and bilateral infiltrates seen on the chest X ray.

created by PCR cloning and serially diluted. As an inhibition control, distinct copies of the cloned amplicons were added to the DNA extracted from the two samples of the pericardial effusion. The samples were analyzed in duplicate, and PCRs were repeated twice.

Only the *C. pneumoniae* PCR gave positive results with both samples. For detection of the *C. pneumoniae*-specific region of the *rpoB* gene (AE002228), primers Cp3-for (5′-GCT CCC AGC TTT CGC AGT T-3′) and Cp3-rev (5′-GCA CAA AGA CGT CGT TTG TGA GT-3′) were used, delimiting a 72-bp DNA segment and flanking the binding region of the fluorogenic probe (5′-6-carboxyfluorescein-TGG ACC AAA CCA ACC CTG TAG CTG AGT T′-6-carboxytetramethylrhodamine). Species specificity of the PCR was ensured, as DNA of *C. trachomatis* and *C. psittaci* was not amplified (data not shown).

As depicted in Fig. 3 the sensitivity of the *C. pneumoniae* TaqMan PCR was found to be <50 copies/assay. With regard to the dilution used in PCR, the detected 30 copies of *C. pneumoniae* genomes in sample 1 corresponded to 2.4×10^4 *C. pneumoniae* cells per ml of pericardial effusion, while the copy number in sample 2 amounted to one-fourth of that amount.

Chlamydia pneumoniae, recently renamed *C. pneumoniae* (2), is a frequent cause of community-acquired respiratory

FIG. 2. Two-dimensional echocardiogram from an apical four-chamber view shows a large pericardial effusion.

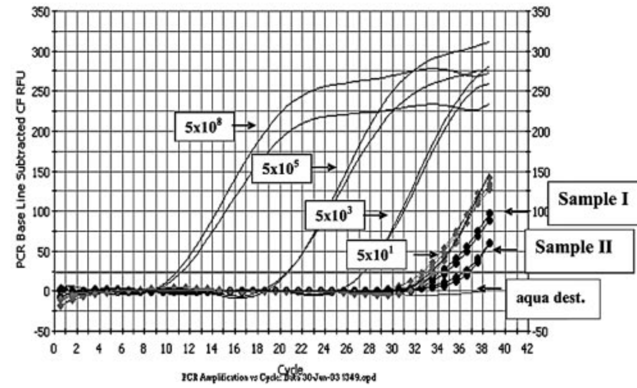

FIG. 3. Detection of *C. pneumoniae* by TaqMan PCR. DNAs of samples I and II, each corresponding to 5 μl of the pericardial effusion, were subjected to a *C. pneumoniae*-specific TaqMan PCR with (gray curves with rhombs) and without (black curves with dots) spiking with 100 copies of the Cpneu plasmid. In parallel, serial dilutions of the Cpneu plasmid were amplified to enable quantification of the PCR; aqua destillata. was used as a negative control. The numbers represent copies per 25-μl PCR mixture.

tract infections, including pneumonia and bronchitis. It has also been associated with endocarditis and myocarditis (4, 6, 10), but there is just one report of an immunocompromised adult patient with *C. pneumoniae* pneumonia and concurrent acute hemorrhagic pericarditis (15). Our patient showed serologic signs of a *C. pneumoniae* infection, with positive test results for IgA and IgG antibodies in the serum and a positive PCR result for the pericardial effusion. Chronic infection with *C. pneumoniae* has been considered a risk factor for coronary heart disease, since a close association was reported between high levels of *C. pneumoniae*-specific IgA antibodies and an increased risk of myocardial infarction (9). Gnarpe et al. found a significantly increased level of IgA antibodies in patients with myocarditis, perimyocarditis, or pericarditis compared to the results seen with healthy blood donors of the same age (4). Although no quantitative IgA antibody levels were measured for our patient, this case report supports the notion that *C. pneumoniae* may be associated with inflammatory heart disease. There is still discussion concerning the diagnostic "gold standard" of *C. pneumoniae* infection, and the choice of diagnostic tests is of utmost importance when evaluating a possible relationship between *C. pneumoniae* and a particular disease (7, 12). Hermann et al. showed that ELISAs are fast and objective and deliver seroprevalence results, sensitivities, and specificities that are very similar to those of the microimmunofluorescence assay, which is widely used as a serological test for demonstration of the presence of *C. pneumoniae* antibodies (5) With an IgA and IgG seropositivity result and the detection of *C. pneumoniae* genome equivalents in the pericardial fluid by PCR, we describe for the first time the uncommon finding of *C. pneumoniae* acting as a probable direct inducer of pericardial inflammation during *C. pneumoniae* infection.

For children with community-acquired pneumonia it is commonly difficult to obtain specimens for culture, and results may be misleading due to contamination with unrelated infective agents. Culture and subsequent PCR testing for *C. pneumoniae*, which is the most sensitive method for detection of *C.*

pneumoniae, are not generally available and take many days before results are confirmed. Acute- and convalescent-phase serum specimens for antibody titer determinations to selected pathogens can be obtained to confirm etiology, but results are not available during acute illness. The most common causes of pericarditis in children are purulent disease (40%), collagen vascular disease (30%), viral disease (20%), and neoplastic disease (10%) (8). Empirical antibiotic treatment of pneumonia with concurrent pericarditis should be directed towards the most common causes (3). Wubbel et al. found no difference in effectiveness of antibiotics (azithromycin versus amoxicillin-clavulanic acid or erythromycin) in patients with community-acquired pneumonia, even among those with infection attributed to *M. pneumoniae*, *C. pneumoniae*, and *S. pneumoniae* (14). Until additional information is available the selection of an antimicrobial agent for therapeutic treatment of children with community-acquired pneumonia should be based on clinical judgment. Azithromycin is active against a wide range of organisms responsible for community-acquired pneumonia and has pharmacokinetics and tolerance superior to those of erythromycin (11, 14). Moreover, results from initial studies conducted with cystic fibrosis patients suggest anti-inflammatory action resulting from macrolide therapy (13). For our patient with concurrent hemorrhagic pericarditis, azithromycin therapy led to complete resolution of clinical findings.

Pericardial drainage may also be required for treatment of patients with pericardial effusion with cardiac tamponade and may provide diagnosis of the causative agent. It must be emphasized that antimicrobial therapy alone would be mostly insufficient for the treatment of purulent pericarditis (13). There are no data about standardized treatment of hemorrhagic pericarditis. Although percutaneous pericardial drainage is a rather straightforward procedure, there is an ongoing discussion whether pericardial drainage should routinely be performed with patients who have a large pericardial effusion without tamponade (1).

The presented case report suggests that differential diagnosis of hemorrhagic pericarditis in patients with pneumonia should include *C. pneumoniae* as a causative agent. In addition to diagnostic and therapeutic pericardial drainage, empirical therapy with azithromycin seems appropriate.

REFERENCES

1. **Cakir, O., F. Gurkan, A. E. Balci, N. Eren, and B. Dikici.** 2002. Purulent pericarditis in childhood: ten years of experience. J. Pediatr. Surg. **37:**1404–1408.
2. **Everett. K. D., R. M. Bush, and A. A. Andersen.** 1999. Emended description of the order Chlamydiales, proposal of Parachlamydiaceae fam. nov. and Simkaniaceae fam. nov., each containing one monotypic genus, revised taxonomy of the family Chlamydiaceae, including a new genus and five new species, and standards for the identification of organisms. Int. J. Syst. Bacteriol. **2:**415–440.
3. **Fairley, C. K., M. Ryan, P. G. Wall, and J. Weinberg.** 1996. The organisms reported to cause infective myocarditis and pericarditis in England and Wales. J. Infect. **32:**223–225.
4. **Gnarpe, H., J. Gnarpe, B. Gastrin, and H. Hallander.** 1997. *Chlamydia pneumoniae* and myocarditis. Scand. J. Infect. Dis. (Suppl.). **104:**50–52.
5. **Hermann, C., K. Gueinzius, A. Oehme, S. Von Aulock, E. Straube, and T Hartung.** 2004. Comparison of quantitative and semiquantitative enzyme-linked immunosorbent assays for immunoglobulin G against *Chlamydophila pneumoniae* to a microimmunofluorescence test for use with patients with respiratory tract infections. J. Clin. Microbiol. **42:**2476–2479.
6. **Norton, R., S. Schepetiuk, and T. W. Kok.** 1995. *Chlamydia pneumoniae* pneumonia with endocarditis. Lancet **345:**1376–1377.
7. **Persson, K., and J. Boman.** 2000. Comparison of five serologic tests for diagnosis of acute infections by *Chlamydia pneumoniae*. Clin. Diagn. Lab. Immunol. **7:**739–744.
8. **Roodpeyma, S., and N. Sadeghian.** 2000. Acute pericarditis in childhood: a 10-year experience. Pediatr. Cardiol. **21:**363–367.
9. **Saikku, P., M. Leinonen, L. Tenkanen, E. Linnanmaki, M. R. Ekman, V. Manninen, M. Manttari, M. H. Frick, and J. K. Huttunen.** 1992. Chronic *Chlamydia pneumoniae* infection as a risk factor for coronary heart disease in the Helsinki Heart Study. Ann. Intern. Med. **116:**273–278.
10. **Tong, C. Y., F. Potter, E. Worthington, and P. Mullins.** 1995. *Chlamydia pneumoniae* myocarditis. Lancet **346:**710–711.
11. **Vergis, E. N., A. Indorf, T. M. File, Jr., J. Phillips, J. Bates, J. Tan, G. A. Sarosi, J. T. Grayston, J. Summersgill, and V. L. Yu.** 2000. Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients: a prospective, randomized, multicenter trial. Arch. Intern. Med. **160:**1294–1300.
12. **Verkooyen, R. P., D. Willemse, S. C. Hiep-van Casteren, S. A. Joulandan, R. J. Snijder, J. M. van den Bosch, H. P. van Helden, M. F. Peeters, and H. A. Verbrugh.** 1998. Evaluation of PCR, culture, and serology for diagnosis of *Chlamydia pneumoniae* respiratory infections. J. Clin. Microbiol. **36:**2301–2307.
13. **Wolter, J. M., S. L. Seeney, and J. G. McCormack.** 2002. Macrolides in cystic fibrosis: is there a role? Am. J. Respir. Med. **1:**235–241.
14. **Wubbel, L., L. Muniz, A. Ahmed, M. Trujillo, C. Carubelli, C. McCoig, T. Abramo, M. Leinonen, and G. H. McCracken, Jr.** 1999. Etiology and treatment of community-acquired pneumonia in ambulatory children. Pediatr. Infect. Dis. J. **18:**98–104.
15. **Zver, S., M. Kozelj, and P. Cernelc.** 1997. *Chlamydia pneumoniae* pneumonia with acute hemorrhagic pericarditis in patient with acute leukemia. Haematologica **82:**254.